Antimicrobial Susceptibility Testing: What’s New from CLSI (also CMS and FDA)

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What’s New from CLSI (AST)
- New 2015 AST documents:
  - M100 - S25
  - M02 - A12
  - M07 - A10
- Many of the changes involve reformatting, streamlining, and clarification of recommendations.
- New carbapenemase test - Carba NP
- No new breakpoint changes (but new drugs from FDA)
- Big bombshell is from CMS regarding the use of CLSI references in CLIA survey guidelines for AST QC.

Question for You
- How often do you perform AST QC?
  - Daily?
  - Weekly?

CLIA QC Regulations: General QC (493.1256)
- Perform control procedures using the number and frequency specified by the manufacturer as long as the recommendations meet CLIA minimums:
  - Perform at least once each day the test is performed.
  - For quantitative procedure, include two levels of control materials.
  - For qualitative procedure, include a negative and positive control.

CLIA Regulations: Bacteriology (493.1261)
- For antimicrobial susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antimicrobial agent(s) before, or concurrent with, initial use, using approved control organisms.
- Each day tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.
- The laboratory’s zone sizes or minimum inhibitory concentration for control organisms must be within established limits before reporting patient results.

Quality Control - AST
- Most clinical labs currently perform weekly AST QC based on CLSI recommendations as published in M100.
- CMS accepted the CLSI recommendations by referencing them in the CLIA Survey Procedures and Interpretive Guidelines (IGs).
- IGs allow accrediting agencies with CLIA deemed status such as CAP to accept exceptions to the default CLIA QC rules.
- Examples:
  - Weekly AST QC
  - Streamlined identification QC
Quality Control Plans

- QCP - Quality Control Plan
- EQCP - Equivalent QCP (no longer acceptable as of January 2016)
- IQCP - Individualized QCP (required as of January 2016 if laboratory wants to do less than CLIA minimum QC)
- IQCP are voluntary but are required if QC is modified
- Two year education and transition period began in January 2014

CLIA IG Changes

- On January 9, 2015 CMS published an advanced copy of the survey procedures for laboratories that removed CLSI standards and guidance for the IGs.
- A letter to State Survey Agency Directors communicating this went out in October 31, 2014.
- As of January 2016, microbiology laboratories will have two options for CLIA QC:
  - Follow the CLIA QC regulations
  - Implement an IQCP
- California State never accepted EQCP, still working on CLIA 2003 changes....

Individualized Quality Control Plan (IQCP)

- Every laboratory has some type of QCP.
  - May be a very high level document
  - QC specifics probably incorporated into specific assay procedures
- CLSI EP-23A – Laboratory Quality Control Based on Risk Management (2011)

What Is Risk Management?

- Comprehensive process to identify and rank potential assay failures/errors so that appropriate mitigations can be implemented and the failures/ errors prevented.
- Goals are:
  - Reduce the risk of failures/errors
  - Implement processes and procedures that prevent or detect failures/errors before harm occurs
  - Includes preexamination, examination, and postexamination phases of testing

Risk Management

- Very familiar to manufactures of IVDs
- Risks are assessed for every assay during every phase of product development and management.
  - Formal process (can be reviewed by FDA during inspections)
    - Reviewed at least 4-6 times during product development
    - Revisited as part of corrective actions
  - Every changing templates
  - Quantitative rankings for severity, occurrence, and detectability
**IQCP Requirements**

- An IQCP requires:
  - Risk Assessment (assess risks, plan mitigations)
  - Data (past QC records, verification studies, previous corrective action, manufacturer’s information, proficiency testing, publications??)
  - Quality Assessment (QA)
- Will California accept an IQCP?
- CA did not accept EQCPs
- CAP and other CLIA deemed status agencies will need to incorporate IQCPs into their checklists.

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**CLSI AST Subcommittee Working Group**

- Ad hoc WG created to help laboratories deal with AST QC
- First meeting was at January AST Subcommittee meeting.
- Susan Munro is leading the effort along with Susie Sharp and Janet Hindler along with other clinical microbiologists.
- CMS and AST device manufacturers are also represented.
- Plan is to create a template that laboratories can use to create their own IQCP for AST.
- Will be posted on-line at CLSI.org and probably ASM.org as well.
- Goal is to have them posted in May.
- ASM Special Session on IQCP for AST, ID systems, and media

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**Carba NP Test**

- Carbapenemase confirmation test for Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter species
- Better (more specific and sensitive than Modified Hodge Test) and can be used for P. aeruginosa and Acinetobacter species as well as Enterobacteriaceae
- Easy to perform (once reagents are prepared)
- Available commercially from BioMerieux OUS
- NP – Nordmann – Poirel


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**Carba NP**

- Mayo Clinic has published on this and provided their data to CLSI to support publication of a generic method in M100
- Used microtubes rather than microtiter plate
- Five reagents (directions included)
  - Phenol red solution (Solution A) – good for 2 weeks
  - Carbapenen solution (Solution B) – good for 3 days only
  - Incubation up to 2 hours (if positive earlier – OK to report)

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**Mayo Results**

<table>
<thead>
<tr>
<th>All Isolates</th>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carb NP</strong></td>
<td><strong>MHT</strong></td>
</tr>
<tr>
<td>CA</td>
<td>209</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100 (96.4-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (97.4-100)</td>
</tr>
<tr>
<td>PPV</td>
<td>100 (96.4-100)</td>
</tr>
<tr>
<td>NPV</td>
<td>100 (96.4-100)</td>
</tr>
</tbody>
</table>

**Carba NP**

- Do you have to do the Carba NP confirmation?
- No, especially if you are using the latest carbapenem breakpoints
  - Enterobacteriaceae – published in 2010
  - Pseudomonas aeruginosa – published in 2012
  - Acinetobacter species – published in 2014
- Not needed for individual patient care
- Good to know for infection prevention

**New Drugs/New Breakpoints?**

- Nothing from CLSI in this years M100-S25 document but four new antimicrobial agents were approved by FDA in 2014.
  - Tedizolid (Sivextro) – Cubist Pharmaceuticals
  - Oxazolidone
  - Dalbavancin (Dalvance) – Durata Therapeutics
  - Lipoglycopeptide
  - Oritavancin (Orbactiv – The Medicines Company)
- Lipoglycopeptide
  - Ceftolozane/tazobactam (Zerbaxa - Cubist Pharmaceuticals)
  - Cephalosporin/beta-lactamase inhibitor combination

**Tedizolid**

- 2nd generation oxazolidinone (more potent than linezolid against MRSA); oral or IV administration
- Acts by inhibition of protein synthesis
- Approved by FDA June 2014 for the treatment of acute bacterial skin and skin structure infections caused by:
  - Staphylococcus aureus (MRSA and MSSA)
  - Streptococcus pyogenes
  - Streptococcus agalactiae
  - Streptococcus anginosus group
  - Enterococcus faecalis
- Has activity against some linezolid resistant S. aureus and VRE (no FDA approved indications)

**Lipoglycopeptides**

- Glycopeptide: Vancomycin
- Lipoglycopeptides:
  - Dalbavancin* (Dalvance - FDA approved May 2014)
  - Oritavancin* (Orbactiv - FDA approved August 2014)
  - Teicoplanin (Used outside US)
  - Televancin* (Vibactiv - FDA approved 2009)
  - Ramoplanin (in development for C. diff)
- Lipoglycopeptides have lipophilic sidechains that can make them extremely sticky
  - * Polysorbate-80 (Tween) added to broth for testing

**Dalvancin**

- Lipoglycopeptide; IV administration only
- Acts by inhibition of cell wall synthesis
- Approved by FDA May 2014 for the treatment of acute bacterial skin and skin structure infections caused by:
  - Staphylococcus aureus (MRSA and MSSA)
  - Streptococcus pyogenes
  - Streptococcus agalactiae
  - Streptococcus anginosus group
- Two dose regimen – doses are one week apart

**Tedizolid FDA Breakpoints**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
<th>Disk Diffusion Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Staphylococcus aureus (MRSA and MSSA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus anginosus group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Gram-positive (G+) bacteria

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  - Streptococcus agalactiae
  - Streptococcus anginosus group
- Two dose regimen – doses are one week apart
Oritavancin

- Lipoglycopeptide; IV administration only
- Acts by inhibition of cell wall synthesis
- Approved by FDA May 2014 for the treatment of acute bacterial skin and skin structure infections caused by:
  - Staphylococcus aureus (MRSA and MSSA)
  - Streptococcus pyogenes
  - Streptococcus agalactiae
  - Streptococcus dysgalactiae
  - Streptococcus anginosus group
  - Enterococcus faecalis (vancomycin-susceptible isolates only)

Oritavancin FDA Breakpoints

- Single dose regimen
- In vitro activity reported against most VRE and VRSA

Telavancin

- Lipoglycopeptide; IV administration only (once a day dosing)
- Acts by inhibition of cell wall synthesis
- Approved by FDA in 2009 for:
  - Complicated bacterial skin and skin structure infections caused by:
    - Staphylococcus aureus (MRSA and MSSA)
    - Streptococcus pyogenes
    - Streptococcus agalactiae
    - Streptococcus dysgalactiae
    - Enterococcus faecalis (vancomycin-susceptible isolates only)
  - Hospital-acquired and ventilator-associated bacterial pneumonia caused by:
    - Staphylococcus aureus (MRSA and MSSA)

Telavancin Black Box Warnings

- Patients with pre-existing moderate/severe renal impairment (CrCl <30 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl <30 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk. (6.1)
- Nephrotoxicity. New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (6.2)
- Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (6.4, 8.1)
- Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (6.1)
- Adverse developmental outcomes observed in 3 animal species at clinically relevant doses, rashes, and concerns about potential adverse developmental outcomes in humans. (6.1)
Televancin FDA Breakpoints

Table 9: Susceptibility Interpretive Criteria for Televancin

<table>
<thead>
<tr>
<th>Susceptibility Interpretive Criteria (mg/L)</th>
<th>Disk Diffusion Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S I R</td>
<td>S I R</td>
</tr>
<tr>
<td>S. aureus (including methicillin-resistant isolates)</td>
<td>≤ 0.12 – – 2 15 – –</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>≤ 0.13 – – 0.65 – –</td>
</tr>
<tr>
<td>Streptococcus anginosus</td>
<td>≤ 0.15 – – 0.25 – –</td>
</tr>
<tr>
<td>Enterococcus faecalis (vancomycin-resistant isolates only)</td>
<td>≤ 0.25 – – 0.5 – –</td>
</tr>
</tbody>
</table>

1. The current absence of resistant isolates precludes defining any results other than “susceptible.” Isolates yielding results other than susceptible should be subjected to additional testing.

Ceftolozane/tazobactam

- Cephalosporin/beta-lactamase inhibitor combination; IV administration only; q8 hour dosing
- Ceftolozane acts by inhibition of cell wall synthesis; tazobactam acts by inhibiting beta-lactamases
- Approved by FDA in December 2014 for:
  - Complicated intra-abdominal infections
    - Used with metronidazole for anaerobes
  - Complicated urinary tract infections including pyelonephritis

Ceftolozane/tazobactam

- Complicated intra-abdominal infections caused by:
  - Enterobacter cloacae
  - Escherichia coli
  - Klebsiella oxytoca
  - Klebsiella pneumoniae
  - Proteus mirabilis
  - Pseudomonas aeruginosa
  - Bacteroides fragilis
  - Streptococcus anginosus
  - Streptococcus constellatus
  - Streptococcus salivarius

- Complicated urinary tract infections and pyelonephritis caused by:
  - Escherichia coli
  - Klebsiella pneumoniae
  - Proteus mirabilis
  - Pseudomonas aeruginosa

- Ceftolozane has good activity against Pseudomonas aeruginosa including some ceftazidime and carbapenem resistant strains.
- Tazobactam extends activity against some ESBLs and anaerobes - but not CRE

Ceftolozane/tazobactam FDA Breakpoints

Table 7: Susceptibility Interpretive Criteria for Ceftolozane/Tazobactam

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentration (mcg/mL)</th>
<th>Disk Diffusion Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≤ 2</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>≤ 4</td>
<td>8</td>
</tr>
<tr>
<td>Streptococcus anginosus</td>
<td>≤ 8</td>
<td>16</td>
</tr>
</tbody>
</table>

FDA Approvals 2015

- Already one new antimicrobial agent approval for 2015
- Ceftazidime-avibactam (Avycaz)
  - The second cephalosporin/beta-lactamase inhibitor combination to gain FDA approval
- Avibactam
  - First non-beta-lactam beta-lactamase inhibitor
  - Diazabicyclooctane

HQ:  O  S  O  N  O  N  S  N  NH₂
Avibactam inhibits a broader range of beta-lactamases than the beta-lactam beta-lactamase inhibitors
- Class A – ESBL and KPCs
  - ESBLs: TEM, SHV, CTX-M
- Class C – AmpC
- Class D – OXA
- Not active against Class B – metallo-beta-lactamases
  - NDMs
  - VIMs
  - IMPs

Ceftazidime/avibactam
- Cephalosporin/beta-lactamase inhibitor combination; IV administration only
- Ceftazidime acts by inhibition of cell wall synthesis; avibactam acts by inhibiting beta-lactamases
- Approved by FDA in February 2015 for:
  - Complicated intra-abdominal infections in combination with metronidazole
  - Complicated urinary tract infections including pyelonephritis

Complicated intra-abdominal infections caused by:
- Escherichia coli
- Enterobacter cloacae
- Klebsiella pneumoniae
- Klebsiella oxytoca
- Proteus mirabilis
- Providencia stuartii
- Pseudomonas aeruginosa

Complicated urinary tract infections and pyelonephritis caused by:
- Citrobacter freundii
- Citrobacter koseri
- Escherichia coli
- Pseudomonas aeruginosa
- Enterobacter aerogenes
- Enterobacter cloacae
- Proteus species
- Klebsiella pneumoniae

Ceftazidime/avibactam
- FDA Breakpoints
- Other combination antimicrobial agents in the pipeline:
  - Ceftaroline/avibactam
  - Imipenem/relebactam (Class A and C)
  - Aztreonam/avibactam
  - Meropenem/RPX7009 (boronic beta-lactamase inhibitor, Class A including KPC)

FDA – One Step Forward, Two Steps Back
- FDA CDER (Drugs)
  - More antimicrobial agents in the pipeline than previously thanks to the GAIN Act and procedural improvements.
  - Breakpoints?
  - Intermediates?
  - Species specificity varies (only S. aureus)
  - Breakpoint change table has disappeared?
  - Labeling information harder to locate
- FDA CRHD (Devices)
  - Still very difficult if not impossible to get some of the revised breakpoints cleared by FDA
**Cefazolin Saga**
- Poster antimicrobial agent for unintended consequences
- First generation cephalosporin
- Good activity against both staphylococci and gram-negatives
- Often used for surgical prophylaxis
- Good tract record for use during pregnancy
- CLSI breakpoint first changed in 2010 to address ESBL issues
- AST Subcommittee did not want labs to report isolates as S to cefazolin and resistant to 3rd generation cephalosporins.

**Cefazolin Issues**
- Concern was raised the next year that the new breakpoints were overall resistance.
- Cefazolin was used to treat UTIs with potential pyelonephritis in pregnancy.
- Data was presented showing efficacy and breakpoints were raised one dilution.

**Cefazolin (Reference Results)**
- Population distribution (EUCAST.org) with FDA Breakpoints

**Cefazolin with FDA Breakpoints**
- VME 0
- ME 0
- Min 35 (18.7%)
- CA 81.3%

**Cefazolin with CLSI Breakpoints**
- VME 3 (1.9%)
- ME 0
- Min 36 (19.3%)
- CA 80.7%
Cefazolin Saga

- If the reference method (frozen broth microdilution) does not meet FDA requirements, how can a device ever hope to?

Cefazolin - UTI Breakpoints

- In 2014 M100-S24, CLSI published cefazolin breakpoints to be used to predict ("as a surrogate for") oral cephems used in the treatment of uncomplicated UTIs:
  - Oral cephems include: cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalaxin, and loracarbef
  - Organisms: E. coli, K. pneumoniae, and P. mirabilis
- In 2016, there will be a UTI breakpoint for cefazolin itself in the same box as the new systemic breakpoints.

Cefazolin - UTI Breakpoints

- Cephems (Parenteral)
  - Cefazolin ≤ 2 S 4 I ≥ 8 R
  - Cefazolin uUTI ≤ 16 S ≥ 32 R
- Cephems (Oral)
  - Cefazolin ≤ 16 S ≥ 32 R
  - "Surrogate test for oral cephem in uUTI"

Cefazolin with CLSI uUTI Breakpoints

<table>
<thead>
<tr>
<th>Cefazolin</th>
<th>Ampicillin</th>
<th>Cephalaxin uUTI</th>
<th>Oral Cephems</th>
<th>Ciprofloxacin</th>
<th>Trimethoprim/sulfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8 S</td>
<td>≤ 16 S</td>
<td></td>
<td></td>
<td>≤ 1 S</td>
<td>≥ 4 R</td>
</tr>
</tbody>
</table>

VME 2 (1.1%)
ME 3 (1.6%)
CA 97.3%

AST - Always of Interest

- Reporting Results: Urine Isolate Example

Urine culture: ≥ 100,000 CFU/mL

- Escherichia coli
  - Ampicillin ≤ 8 S
  - Cefazolin uUTI ≤ 16 S
  - Oral Cephems S
  - Ciprofloxacin ≤ 1 S
  - Trimethoprim/sulfa ≥ 4 R